

REMARKS

Applicants would like to thank the Examiner for taking the time to conduct a phone interview on August 18, 2004, during which the 35 U.S.C. 103(a) rejection was discussed. Claims 1-3, 5, and 22-24 and pending in the instant application. Claim 1 has been amended without prejudice or acquiescence in order to advance prosecution of the instant application.

The issues outstanding in the present application are as follows:

- Claims 1-3, 5, and 22-24 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.
- Claims 1-3, 5, and 22-24 have been rejected under 35 U.S.C. § 103(a) as allegedly being anticipated by U.K. Patent Application GB 2 294 692 A, Wong *et al.*, GB 2 306 485 A, Wong *et al.*, U.S. Patent No. 6,117,661, Wong *et al.*, or U.S. Patent No. 6,100,074, Flitsch *et al.*

I. 112, indefiniteness rejection

The Examiner has rejected claims 1-3, 5, and 22-24 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claim 1 has been amended, and the rejection is moot. Applicants respectfully request reconsideration of the 35 U.S.C. § 112 rejection.

II. 103, obviousness rejections

The Examiner has rejected claims 1-3, 5, and 22-24 as allegedly being obvious over GB A 2294692, GB A 2306485, US Patent No. 6,117,661 and U.S. Patent No. 6,100,074. Applicants respectfully traverse.

Applicants respectfully submit that, while it is often obvious for one of ordinary skill in the art to search for a solution, the actual solution or discovery is rarely, if ever, obvious, and that the outstanding rejection is an application of an “obvious to try” standard. The “obvious to try” standard has been held to constitute an improper ground for a 35 USC § 103 rejection, for example *In re O’Farrell*, 858, F.2d 894, 903 (Fed. Cir. 1988):

“The admonition that ‘obvious to try’ is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.”

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Applicants refer the Examiner to the Declaration from the inventor in support of the argument that the cited references do not provide a reasonable expectation of success.

The teachings of the cited references do not provide a basis for predicting the success of oxidation reactions of the mutant enzymes for the claimed class of substrates. The references cited suggest oxidation of entirely different types of compounds than are claimed in the present invention. See attached Declaration for a discussion of the differences between the claimed substrates and the compounds taught by the above references. Thus, one with skill in the art would not expect that oxidation of simple alkyl or aromatic compounds by mutant P450 enzymes could predict the success of oxidation of the claimed substrates by the same enzymes.

Furthermore, the cited references do not provide what one with skill in the art would consider to be adequate information in order to predict the success of potential oxidations of the compounds cited in the references.

NADH consumption and spin-state are not reliable indicators of oxidation, due to “uncoupling,” wherein NADH consumption and change in spin-state of the P450 enzyme becomes “uncoupled” from substrate oxidation product formation. See England *et al* (1998) FEBS Letters 424, 271-4 which states in the second full paragraph of the left hand column of page 272 that: “However, since the monooxygenase activity of P450 enzymes is well known to undergo uncoupling side reactions, not all of the NADH consumed by the system was necessarily utilized for substrate oxidation. It was therefore important to analyse the NADH turnover reactions for the present of substrate oxidation products, and determine the quantities of products formed so that both the rate of product formation and consequently the

coupling efficiency could be calculated.” Also see Atkins and Sligar (1988) J. Biol. Chem. 263, 18842-9 which discusses towards the bottom of the left hand column of page 18846 how the rates of NADH consumption “do not necessarily reflect rates of hydroxylated product formation since various substrate-cytochrome P450 complexes “uncouple” to produce differing amounts of hydrogen peroxide and water resulting from internal branch points within the cytochrome P450 reaction cycle. Also, towards the bottom of the right hand column of page 18848 of Atkins and Sligar, it is noted: “It is interesting, however, that camphane, which elicits a 46% high spin population, results in a drastic reduction in monooxygenase activity such that only 8% of the NADH consumed is utilised for hydroxylation.” Therefore neither change in spin state nor rate of NADH consumption can be used to determine successful oxidation of a compound by a P450 enzyme. Instead detection of the oxidised product is required to determine whether a compound is oxidised by a P450 enzyme. Thus the spin data or NADH consumption data in the cited documents cannot be used to infer that successful oxidation is occurring.

Similarly, the DTT data which is provided in the cited documents is a measure of the displacement by a test compound of DTT which is bound to the P450 enzyme (see third paragraph of page 12 of GB-A-2294692). The mere binding of a compound to a P450 enzyme cannot be used to determine whether or not oxidation of the compound occurs, as again an uncoupled reaction may occur instead.

Thus the references cited by the Examiner cannot be interpreted as demonstrating to one with skill in the art that mutant P450 enzyme are able to oxidize a wide range of substrates. Applicants note that whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986.

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A check in the amount of \$210 is attached to cover the fee for a two-month extension of time. Applicant believes no additional fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02196US0 from which the undersigned is authorized to draw.

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Respectfully submitted,

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